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10/637,159	08/08/2003	J. Mark Weber	065382-0006	2929

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EXAMINER

CHOWDHURY, IQBAL HOSSAIN

ART UNIT	PAPER NUMBER
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1652

MAIL DATE	DELIVERY MODE
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10/30/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/637,159

Applicant(s)

WEBER ET AL.

Examiner

Iqbal H. Chowdhury, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 2-7, 12-14 and 27-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 8-11, 15-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 8/8/2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- 1) ☐ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-34 are currently pending and under consideration in the instant application.

Restriction/Election

Applicant's election without traverse of Group XXIII, Claim(s) 1, 8-11, and 15-26, drawn to a method of increasing the production of antibiotic either polyketide or macrolide biologically active compound, in a cell wherein the biologically active compound is derived at least in part from methylmalonyl-CoA, the method comprising the step of inhibiting the activity of methylmalonyl-CoA mutase by reducing level of cofactor coenzyme B12 by inhibiting the transcription of cob gene and erythromycin as species in the response filed on 9/27/2007 is acknowledged.

Applicants request for clarification for withdrawing previous restriction requirement mailed on 3/21/2007. As discussed in the previous office action, the supplemental requirement was at the discretion of the examiner (see MPEP 802 and 37 CFR 1.142) and was deemed appropriate and necessary in view of the plurality of claimed patentably distinct inventions.

Claims 2-7, 12-14, 27-34 and are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1, 8-11 and 15-26 are at issue and are present for examination.

Priority

Applicants do not claim for priority of any Application submitted previously.

Information Disclosure Statement

The information disclosure statement (IDS) is not submitted with this application.

Drawings

Drawings submitted on 8/8/2003 are objected by the Examiner for the recitation of the nucleic acid sequences without appropriate sequence identifiers i.e. SEQ ID NOs. Examiner urges the applicants to provide sequence identifiers in response to this Office action. See particularly 37 CFR 1.821(d).

Claim Objections

Claim 26 is objected to in the recitation "cob"; as abbreviations should not be used without at least once fully setting forth what they are used for. Examiner suggests appropriate correction.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the

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recitation of "biologically active" as it is unclear what the scope of activities that is encompassed by this term. On page 8 of the specification, applicants define the term "biologically active" as "any compound having an effect on a living organism". However, it is still not clear to the Examiner as to what type of "effects" or "activities" are encompassed. Therefore, the scope of the phrase "biologically active compound" is vague and indefinite. Accordingly, claims 8-11 and 15-26 are rejected, as they are dependent on claim 1.

Claim 1 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation "increasing the biologically active compound", which is confusing. The metes and bounds of the term "increasing" are not clear to the Examiner. It is not clear as to how one skilled in the art can determine whether production of biologically active compound is increased without comparing it with a control. The Examiner requests clarification. Accordingly, claims 8-11 and 15-26 are rejected, as they are dependent on claim 1.

Claim 1 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite and vague in the recitation of "at least in part", in the context of methylmalonyl-CoA. The metes and bounds of the term "at least in part" are not clear to the Examiner. It is not clear as to how one skilled in the art can determine whether "biologically active

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compound" is derived at least in part from methylmalonyl-CoA. Accordingly, claims 8-11 and 15-26 are rejected as they depend on claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-11 15-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the production of erythromycin, a biologically active compound, in a *Saccharopolyspora* or *Aeromicrobium* or *Streptomyces*, wherein said erythromycin is derived from methylmalonyl-CoA and the method comprises inhibiting the activity of a methylmalonyl-CoA mutase (MCM) protein encoded by SEQ ID NO 1 and an adenosyltransferase protein encoded by SEQ ID NO: 3 by inhibiting the transcription by mutating said genes (such that the cofactor for MCM is reduced due to inhibiting transcription of SEQ ID NO: 3), does not reasonably provide enablement for a method of increasing the production of any biologically active compound in any or all cells including any plant, animal or bacterial cell, wherein the biologically active compound is derived at least in part from methylmalonyl-CoA and the method comprises inhibiting the activity of said methylmalonyl-CoA mutase (MCM) protein and any adenosyltransferase protein by any method. The specification does not enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, **to make and use** the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breadth of the claims:

Claims 1, 8-11, 15-26 are so broad as to encompass a method of increasing the production of any biologically active compound in any or all cells, wherein the biologically active compound is derived at least in part from methylmalonyl-CoA and the method comprises inhibiting the activity of methylmalonyl-CoA mutase (MCM) enzyme and adenosyltransferase. No correlation between structure and function has been presented.

The amount of direction or guidance presented and the existence of working examples:

The specification discloses a method of increasing the production of erythromycin, a biologically active compound, in *Saccharopolyspora* or *Aeromicrobium* or *Streptomyces*, wherein said erythromycin is derived from methylmalonyl-CoA and the method comprises inhibiting the activity of a methylmalonyl-CoA mutase (MCM) protein encoded by SEQ ID NO 1 and an adenosyltransferase protein encoded by SEQ ID NO: 3 by inhibiting the transcription by mutating said genes (such that the cofactor for MCM is reduced due to inhibiting transcription of SEQ ID NO: 3).

The specification does not support the broad scope of the claims which encompass a method of increasing the production of any biologically active compound in any or all cells including any plant, animal or bacterial cell, wherein the biologically active compound is derived at least in part from methylmalonyl-CoA and the method comprises inhibiting the activity of said methylmalonyl-CoA mutase (MCM) protein and any adenosyltransferase protein by any method because the specification does **not** establish: (A) that any or all cells including animal, plant and bacterial cells will behave as *Saccharopolyspora* or *Aeromicrobium* or *Streptomyces* for producing any biologically compound i.e. polyketides; (B) whether any or all animal, plant and bacterial cell have polyketides biosynthetic pathways as present in *Saccharopolyspora* or *Aeromicrobium* or *Streptomyces*; and (C) whether any or all animal, plant and bacterial cell have appropriate cellular factors, which will permit for efficient production of any biologically active compound i.e. polyketides as present in *Saccharopolyspora* or *Aeromicrobium* or *Streptomyces*; (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The production of polyketides depends on the type of the cell, which has specific PKS biosynthetic gene cluster or host cell factors, which permits efficient expression of PKS genes for heterologous production of polyketides. In general, animal cell lacks PKS biosynthetic gene cluster and heterologous production of polyketides is not advantageous. Therefore, predictability of producing polyketides in specific cells require a knowledge of and guidance with regard to which cells are suitable for producing polyketides and which cell permits bulk biosynthesis of polyketides for commercial purpose by expressing heterologous genes, and detailed knowledge of the ways in which the selection of appropriate host cell relates to its production. In the instant case, the method uses *Saccharopolyspora* or *Aeromicrobium* or *Streptomyces* for producing polyketides such as erythromycin. The art clearly teaches the high level of unpredictability with regard to the heterologous host cell for the production of desired protein remains an empirical and unpredictable process (Pfeifer et al. 2001, p106). The art also clearly teach that *Streptomyces* species are widely used for efficient polyketide biosynthesis not animal cells.

The quantity of experimentation required practicing the claimed invention based on the teachings of the specification:

While methods of producing polyketides in bacterial and fungal host cells were well known in the art at the time of invention, it is not routine in the art to use any plant or any animal cells by trial and error method for producing any biologically active

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compound specifically polyketides with a reasonable expectation of success in obtaining the desired activity/utility is unpredictable.

Conclusion:

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-11, 15-17, and 19-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Vrijbloed et al. (J Bacteriol. 1999 Sep; 181(18): 5600-5). Instant claims are drawn to a method of increasing the production of a biologically active compound in a cell with a methylmalonyl-CoA mutase (MCM) gene encoding enzyme, wherein the

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biologically active compound is derived at least in part from methylmalonyl-CoA and the method comprising inhibiting the activity of a methylmalonyl-CoA mutase (MCM) enzyme by reducing the cofactor for said enzyme or by inhibiting the transcription of said gene by a mutation.

Vrijbloed et al. disclose insertional inactivation of methylmalonyl coenzyme A (CoA) mutase and isobutyryl-CoA mutase genes in *Streptomyces cinnamonensis*, which influence on enhanced polyketide antibiotic biosynthesis. Vrijbloed et al. also teach that the coenzyme B(12)-dependent methylmalonyl-CoA mutase (MCM) catalyze the isomerization of methylmalonyl-CoA to succinyl-CoA, respectively and that mutase has the influence on the conversion of n- and isobutyryl-CoA to methylmalonyl-CoA, which is used as substrate in polyketide biosynthesis by using polyether antibiotic (monensin) producer *Streptomyces cinnamonensis*. Vrijbloed et al. further teach that mutants prepared by inserting a hygromycin resistance gene (hygB) into mutB, encoding the MCM, and the mutB::hygB mutant was unable to grow on propionate and grew only weakly on butyrate and isobutyrate as sole carbon sources. Furthermore, Vrijbloed et al. by using (13)C-labeling experiments show that MCM mutant capable of incorporating butyrate and acetoacetate into the propionate units in monensin A. Monensin is a polyketide, an antibiotic having antifungal and antiparasitic activity and monensin is widely used in animal feed as a major ingredients. Since, *Streptomyces* species naturally produces polyketides including erythromycin, and *Streptomyces* species of Vrijbloed et al. has inactivated mutase gene, which would accumulate methylmalonyl-CoA (by blocking succinyl-CoA biosynthesis), the substrates of many polyketides

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biosynthesis, inside the cell, the *Streptomyces* of Vrijbloed et al. would inherently produce many polyketides including species recited in claim 11 of the instant application. Therefore, Vrijbloed anticipate claims 1, 8-11, 15-17, and 19-26 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vrijbloed et al. (J Bacteriol. 1999 Sep; 181(18): 5600-5) as applied to claims 1-17, 19, 27-31 above, and further in view of Katz et al. (Novel macrolides through genetic engineering, Med Res Rev. 1999 Nov; 19(6): 543-58. Review). Instant claim is drawn to a method of increasing the production of a biologically active compound in *Saccharopolyspora*

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erythraea cell with a methylmalonyl-CoA mutase (MCM) gene encoding enzyme, wherein the biologically active compound is derived at least in part from methylmalonyl-CoA and the method comprising inhibiting the activity of a methylmalonyl-CoA mutase (MCM) enzyme including inhibition, mutation or inactivation.

Vrijbloed et al. teach insertional inactivation of methylmalonyl coenzyme A (CoA) mutase and isobutyryl-CoA mutase genes in *Streptomyces cinnamonensis*, which influence on enhanced polyketide antibiotic biosynthesis. Vrijbloed et al. also teach that the coenzyme B(12)-dependent methylmalonyl-CoA mutase (MCM) catalyze the isomerization of methylmalonyl-CoA to succinyl-CoA, respectively and the influence that mutase has on the conversion of n- and isobutyryl-CoA to methylmalonyl-CoA, which is used as substrate in polyketide biosynthesis by using polyether antibiotic (monensin) producer *Streptomyces cinnamonensis*. Vrijbloed et al. further teach that mutants prepared by inserting a hygromycin resistance gene (hygB) into mutB, encoding the MCM, and the mutB::hygB mutant was unable to grow on propionate and grew only weakly on butyrate and isobutyrate as sole carbon sources. Furthermore, Vrijbloed et al. by using (13)C-labeling experiments show that MCM mutant capable of incorporating butyrate and acetoacetate into the propionate units in monensin A. Monensin is a polyketide, an antibiotic having antifungal and antiparasitic activity. Vrijbloed et al. do not teach using *Saccharopolyspora erythraea* cell for producing polyketide.

Katz et al teach erythromycin, a complex polyketide antibiotic belonging to the macrolide class, is produced as a natural product by the bacterium *Saccharopolyspora erythraea* and the genes encoding the enzymes responsible for the synthesis of said

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antibiotic is cloned and sequenced, and revealing that the polyketide backbone of the molecule is produced by a polyketide synthase (PKS) composed of multifunctional proteins that contain discrete functional domains for each step of synthesis. Katz et al. also teach that genetic manipulation of the PKS-encoding genes can result in predictable changes in the structure of the polyketide component of erythromycin, many of which are not easily achievable through standard chemical derivatization or synthesis and many of the changes can be combined to lead to the further generation of novel structures.

By combining the teachings of Vrijbloed et al. and Katz et al. it would have been obvious to one of ordinary skill in the art at the time of the invention was made to replace *Streptomyces* species with *Saccharopolyspora erythraea* to be used in the method of Vrijbloed et al. for producing polyketide in increased amount.

One of ordinary skill in the art would have been motivated to use *Saccharopolyspora erythraea*, since Katz et al. clearly showed the biosynthesis of novel polyketides (macrolides) by using *Saccharopolyspora erythraea* than other host cells.

One of ordinary skill in the art would have a reasonable expectation of success because Katz et al. teach a successful method of producing novel polyketides/macrolides by using *Saccharopolyspora erythraea*.

Therefore, the above references render the claim 18 *prima facie* obvious to one of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 1-34 are pending.

Claims 1-34 are rejected.

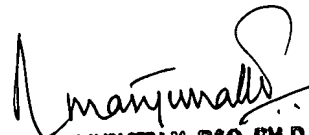
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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